Chronic Ischemic Heart Disease

Introduction

In CAD #1: *Pathophysiology of Atherosclerosis*, we explained the pathogenesis of an atherosclerotic plaque. Symptoms start as the plaque reaches critical stenosis, approximately 70%. This lesson is about those symptoms. There is no rupture and thrombosis, no acute narrowing of the lumen of the artery. The plaque is the necrotic lipid core covered by the fibrous cap. Over decades, the plaque has grown, progressively narrowing the lumen of the artery. That artery is a coronary vessel. Distal to the stenosis, the myocardium is vulnerable to ischemia. Ischemia hurts.

We start this lesson with a detailed look at the symptom of myocardial ischemia, chest pain or angina pectoris, and the two general mechanisms of myocardial ischemia: demand vs. supply ischemia. The rest of this lesson is about deducing whether someone who has chest pain, but not a diagnosis of coronary artery disease, has coronary artery disease. We will walk through the thought processes and clinical reasoning behind the diagnosis, how to make the diagnosis, but not what to do about it. The treatment of chronic ischemic heart disease is discussed in the next lesson. The surgical or interventional management of coronary artery disease is in the last lesson of the series. We conclude this lesson with a discussion of coronary steal and vasospastic angina (best known by its eponym, Prinzmetal's).

Angina Pathology, Demand vs. Supply

Chest pain caused by myocardial ischemia is termed **angina pectoris**. Myocardial ischemia can be caused by two general mechanisms: demand ischemia and supply ischemia. **Demand ischemia** is a result of a chronically narrowed lumen secondary to an atherosclerotic plaque. The lesion has reached critical stenosis, the point at which the narrowed lumen is capable of supplying the myocardium with sufficient oxygen at rest but is incapable of meeting demands with exertion. It can meet demands when myocardial work is low, at rest. It cannot meet demands when myocardial work increases. **Supply ischemia** is caused by an acute narrowing of the lumen diameter secondary to acute plaque rupture and subsequent thrombosis. No matter how little work the heart does, there isn't enough blood flow to supply the myocytes with nutrients. They will die unless the supply is restored.

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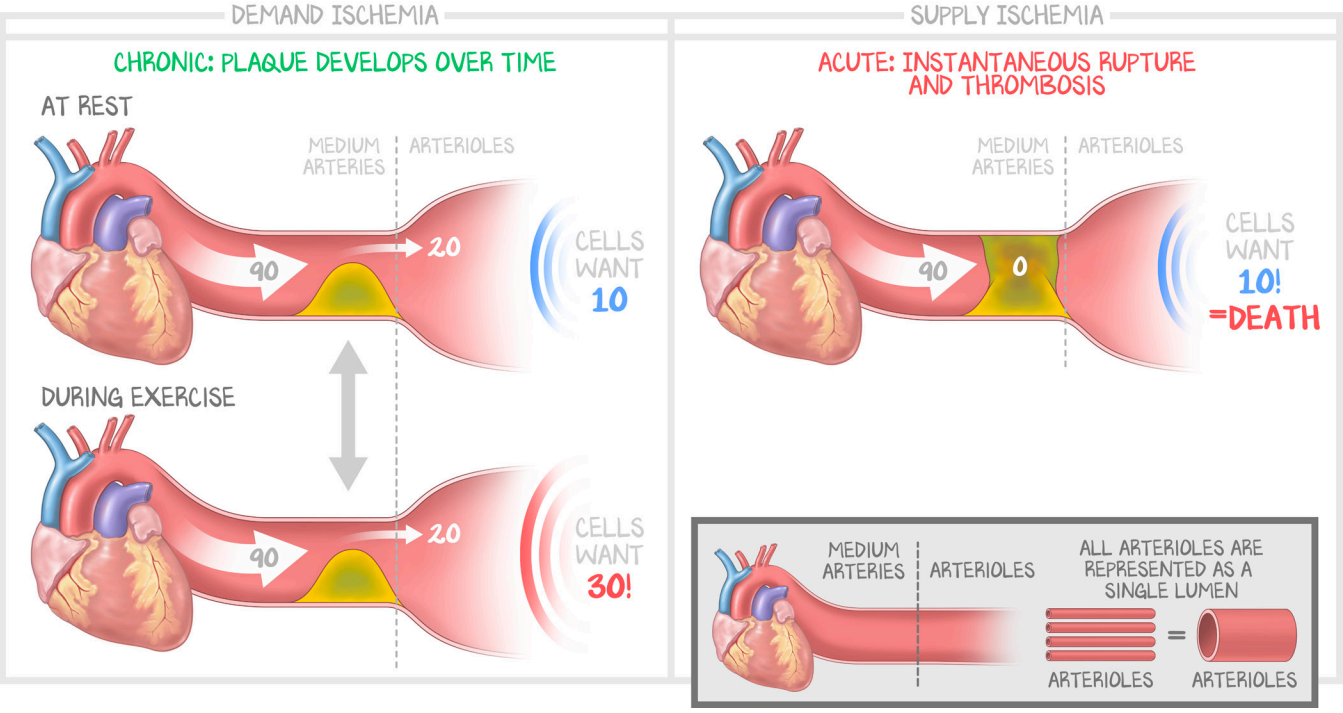

Figure 3.1: Demand vs. Supply Ischemia
In demand ischemia, the vessel diameter doesn't change, but cellular demand does. Because the resistance is set by the plaque and not the arterioles, even though those arterioles dilate, the flow is unchanged. These cells will suffer ischemic injury unless the demand decreases below that permitted by the plaque. In supply ischemia, in this instance a complete and sudden occlusion of the vessel, it doesn't matter how little activity the cells are doing distal to the lesion. If the lesion is not removed, if perfusion not restored, the cells will die.

Said another way, chronic ischemic heart disease is about the progression from a stable atherosclerotic plaque to the provocation of **demand ischemia**. Even though the lumen is narrowed, the patient does not have symptoms at rest. The lumen has narrowed over time, but the ischemia provoked by that stable lesion occurs only when the work of the heart increases. Stable angina is defined by a **fixed lumen diameter** but a **change in myocardial oxygen demand.** If the work is allowed to decrease, if the demand decreases, then the ischemia and angina are alleviated. Chronic ischemic heart disease (aka coronary artery disease) is another way of saying demand ischemia.

In contrast, **supply ischemia** is the ischemia of acute coronary syndrome, of acute rupture and thrombosis of a coronary plaque, with a rapid and acute reduction in the size of a vessel lumen. That thrombosis can partially or completely narrow the lumen. Regardless of its severity, a sudden change in the caliber of the lumen results in a sudden increase in resistance, and therefore a sudden drop in flow, and therefore a sudden drop in supply. The heart doesn't change the work it was doing, doesn't alter the myocardial oxygen demand. There is still insufficient flow, myocardial ischemia, and angina. Because **the luminal diameter suddenly decreases** and **myocardial oxygen demand** doesn't change, it is **supply ischemia.**

There are other ways supply can decrease, such as becoming hypotensive or being without oxygen. But we want you to learn that supply ischemia is due to plaque rupture and acute thrombosis, and therefore acute coronary syndrome. Acute coronary syndrome (aka myocardial infarction) is supply ischemia. Chronic ischemic heart disease (aka coronary artery disease) is demand ischemia.

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INCREASED DEMAND	DECREASED SUPPLY
Increased heart rate	Thrombosis (myocardial infarction)
Increased afterload	Vasospasm (Prinzmetal's angina)
Increased contractility	Oxygen content in the blood (anemia, hypoxemia)
	Hypotension, aortic regurgitation

Table 3.1: Demand and Supply Ischemia
All the ways that ischemia can be provoked, categorized into demand causes and supply causes.

Is It Angina?

Now we take a more clinical turn. A patient complains of chest pain. Is it angina? Do they have coronary artery disease? This is a discussion of the clinical reasoning and the pathophysiology behind it.

Ischemia is caused by an imbalance between the oxygen supply (coronary flow) and demand (myocardial oxygen need). Either reduced flow or increased demand can lead to myocardial ischemia. The extent of that ischemia is determined by how much the flow is reduced (how much of the lumen is occluded) or how high the oxygen demand gets (how hard the heart works). Regardless of its cause, **ischemia provokes angina**. Ischemia is the pathologic process, and angina is the symptom.

An individual will have **nearly identical anginal symptoms** every time **they have ischemia**. However, there is significant variability between patients—one person's anginal symptoms may be completely unlike another's. Even though myocardial ischemia and chest pain are taught as synonyms, some patients' anginal symptoms—their anginal equivalent—may not be pain at all. But the point is that if a patient knows what their stable angina feels like, then they know what their angina due to myocardial infarction feels like because they are the same. "*Is this like your myocardial infarction?*" is a potent predictor of whether their symptoms—be they chest pain or anything else—are caused by myocardial ischemia. Angina pectoris is chest pain. The symptom of myocardial ischemia is chest pain. However, a person can have coronary artery ischemia and infarction but not have chest pain and another symptom is how they experience myocardial ischemia.

Stable angina is the defining characteristic of stable, progressive atherosclerosis. The patient will experience pain when myocardial oxygen demand exceeds the maximum oxygen supply. Being stable, the size of the atherosclerotic plaque does not change. Being stable, the maximum oxygen delivery remains constant minute to minute, day to day. That means that, symptomatically, **the patient knows how far and how fast they can go before symptoms are provoked**. Exertion provokes angina; rest relieves angina. The point is that they have a limit, a maximum amount of exertion they can take, a maximum amount of work the heart can do before symptoms present. Crossing that line results in symptoms.

Presentation. Classically, angina has been described as **substernal crushing chest pain** that radiates down the arm or up the jaw, is **provoked by exertion**, and is **relieved with nitroglycerin**. These three components are part of the Diamond-Forrester classification. The idea is that exertion brings on the increased myocardial oxygen demand as heart rate and contractility increase. Relief with rest is the same thing—as heart rate and contractility decrease, the myocardial oxygen demand decreases. The relief with nitroglycerin is different. Myocardial oxygen demand is the product of systemic vascular resistance, preload, contractility, and heart rate. Exercise and cessation of exercise increase and decrease heart rate and contractility. Nitroglycerin reduces preload. So, if the person exercises (does any

activity more vigorous than their baseline), increases the heart rate and contractility, and the demand exceeds myocardial oxygen supply (chest pain) but is relieved by nitroglycerin (reduces preload) while maintaining the same level of effort, then there was a demand-supply issue.

The Diamond-Forrester classification has fallen out of favor because of its misuse in chest pain patients in the emergency department. Patients who are having an active myocardial infarction sometimes have **no pain at all** or **their anginal equivalent**. Furthermore, the patients aren't exercising, so rest and exertion cannot be assessed. And if the patient is appropriately given nitroglycerin, the pain may not abate. But the person is still having a heart attack. In the clinic, when the patient is not having an active heart attack, applying the Diamond-Forrester classification is more practical, especially if there were symptoms of angina that came and went. Even then, without the nitroglycerin to reinforce the exertional anginal symptoms, a patient can never practically reach all three criteria. In real life, patients who don't know they have coronary artery disease don't have nitroglycerin, and the people who do have nitroglycerin have it for their known coronary artery disease. But the Diamond-Forrester classification provides a nice way to review the ~~MAP~~ myocardial work equation in the context of coronary ischemia.

One more note on clinical presentation: whenever there are data points—chest pain or not, exertional or not, relieved with nitroglycerin or not—each answer alters the pretest probability of a number of diagnoses on a differential. When seeing a patient with chest pain, you aren't asking, "*is it angina or not?*" (this section's title). Instead, you're asking, *"which of the diagnoses on my differential is this most likely to be?"* You don't just ask the three questions on the Diamond-Forrester checklist, but if all three are present in one patient, the pretest probability of myocardial infarction goes up; if all are negative, the pretest probability goes down. There are more data points to consider after that.

Associated symptoms. Associated symptoms are signs of increased illness. If their anginal equivalent (chest pain) is accompanied by **dyspnea**, **presyncope**, or **diaphoresis**, then the pretest probability of angina goes up—especially if exertion provokes them and rest relieves them. Without chest pain, these symptoms mean very little unless the patient knows that these alone are their anginal equivalent (yes, we are repeating this many times on purpose).

Risk factors. Risk factors are the same as those for atherosclerosis because coronary artery disease is atherosclerosis. **Modifiable risk factors** are hypertension, diabetes, dyslipidemia, obesity, and smoking. **Nonmodifiable risk factors** are age (M > 45, F > 55) and family history. The more risk factors there are and the more severe the risk factors, the more they increase the likelihood of this chest pain being angina.

Physical exam. A patient who is not having symptoms in front of you should have a normal exam. A person with chest pain right now is easier to assess. Pain due to myocardial infarction should be **nonpositional**, **nonpleuritic**, and **nontender**. Nonpositional means the pain is the same with lying down and sitting up. Nonpleuritic means the pain is not exacerbated by taking a deep breath. Nontender means that firm pressure to the site of the chest pain does not alter the pain. Can a person's myocardial infarction be positional, pleuritic, or tender? Absolutely. Especially if their angina has presented that way in the past. But being positional, pleuritic, or tender suggests alternative diagnoses. It doesn't rule out myocardial ischemia, it just makes it less likely because a competing diagnosis becomes more likely.

Labs. In the acute setting, troponin-I and a 12-lead ECG are helpful. In the outpatient setting (how we are approaching this section), a 12-lead can show you a Q wave, indicative of previous infarction, and troponin-I requires hours of ischemia to rise. The two tests performed on essentially every chest pain patient in the emergency department—12-lead ECG and troponin-I—have very limited utility in the clinic, where the patient has no symptoms.

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Making the Diagnosis

This is not a clinical reasoning course, but we put you through that exercise because it is so easy to demonstrate the path of clinical reasoning through such a common condition. Now let's say you do think this person has coronary artery disease, and you want to find out if you are right.

An angiogram is the only test that can confirm or deny the presence of disease. Angiography is the insertion of a wire into an artery (radial or femoral) to thread a catheter to the ostia just outside the aortic valve and inject dye into the coronary arteries. A real-time radiographical video of the contrast is shown to the cardiologist. If the cardiologist identifies defects in coronary filling, the diagnosis is made. If no lesions are found, the diagnosis is rejected. Angiography is definitive but not always the next step. In a patient with evidence of an active myocardial infarction in the emergency department, angiography is performed rapidly, the diagnosis being more certain because of evidence of troponin-I or ST-segment elevation. Angiography requires a specialist (cardiologist) and comes with risk (penetration of a wire into an artery, injection of dye). So unless the diagnosis is practically certain (which is usually not the case), a stress test is the next test.

A **stress test** is the first diagnostic test for a patient whom you think has coronary artery disease but has no evidence of acute disease. A stress test asks, *"is there critical stenosis in a coronary vessel, and is the symptom they are complaining of the cause?"* Be careful how you interpret the results of a stress test. The right question to ask is, *"is there a lesion causing > 70% stenosis that is provoking symptoms?"* The wrong question to ask is, *"is there coronary artery disease?"* A **negative stress test** does not rule out coronary artery disease. But, as of the moment it's performed, it does rule out 70% stenosis, which is the critical stenosis that may rupture and thrombosis, so you can infer that there are no significant lesions. As lesions that aren't 70% stenosed or symptomatic should not be stented (fixed), there is not enough reason to consume resources and place the patient at risk for complications due to an angiogram, so angiography isn't performed. A **positive stress test** does not rule in coronary artery disease, but it definitely means the patient is getting an angiogram to be sure because it is highly probable that they do.

A stress test aims to assess whether the patient has stable angina, which is equal to coronary artery disease, which is equal to chronic ischemic heart disease, which is equal to demand ischemia. Then, the goal is to **increase demand** to **provoke symptoms**, all the while using some method of evaluating the heart to **visualize disease**.

To perform a stress test, there has to be a **stress** and a **test**. Most centers have prefabricated mechanisms—dobutamine echo, dipyridamole nuke, etc. They combine the stress with the test. But you should know that isn't the way it has to be. So we are teaching some of the methods for stressing and some of the methods for testing separately.

Stress needs to get the demand up. The best way is with an **exercise treadmill**. If a patient can walk on a treadmill, then the stress part of the stress test is walking on a treadmill. If there is any reason that the patient cannot walk on a treadmill, then the stress part of the stress test will be **pharmacological therapy**. We want you to focus on dobutamine and dipyridamole. **Dobutamine** increases heart rate and contractility, making the heart work harder (increases demand). **Dipyridamole** does something entirely different, discussed below in coronary steal.

The **test** needs to evaluate the heart. This can be a **12-lead ECG**, **echocardiogram**, or **nuclear study**. As above, most centers have prefab options. At this stage in your training, you're looking for **ST-segment changes** on ECG that occur with symptoms and **lack of movement** on the echo or nuclear—**dead things don't move**. There are reasons to pick one over the other, which we cover in Clinical, but in general, ECG preferred, echocardiogram if the ECG is abnormal at baseline, and nuclear if the echocardiogram is abnormal at baseline.

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"Dead things don't move" is all about myocardial stunning. Stress tests that use imaging look at what happens to the myocardium at rest and stressed. Healthy myocardium contracts under resting conditions and stressed conditions because it does not become ischemic. Already dead myocardium, replaced by scar, will not contract under resting conditions or stressed conditions. You're really after the myocardium at risk. When at rest, there is no ischemia, no myocardial stunning, and the myocardium contracts. Then, under stress, with increased demand, the tissue becomes ischemic and exhibits myocardial stunning. Although not infarcting, not dead scar tissue, myocardial stunning is the phenomenon of ischemic myocardium behaving like scar. **Myocardial stunning** transforms a myocardium that moves at rest to immobile scar under stress.

Coronary Steal

Stenosis is the abnormal narrowing of an artery, usually a discrete segment of an artery, partially obstructing flow. Stenosis can occur through all sorts of mechanisms, but the one most relevant to our discussion is atherosclerosis. The developing plaque grows into the lumen of a vessel, narrowing the lumen of that vessel (stenosis), and resulting in decreased flow through that vessel. As the **radius decreases**, the **resistance increases**. As the resistance increases, the flow decreases.

The development of critical stenosis takes decades. Arterial remodeling attempted to prevent the plaque from causing any stenosis early on in disease. The plaque gradually rises from the luminal surface over time. As the luminal obstruction worsened, with each subsequent expansion of the plaque, there was the subsequent denial of myocardial oxygen and, therefore, arteriolar dilation. By the time there is critical stenosis, the **vessels are maximally dilated at baseline distal to the coronary stenosis**. The plaque has a fixed size. More importantly, the lumen has a fixed size. A lumen with a fixed radius means a fixed resistance, and therefore a fixed flow. The arterioles distal to the lesion cannot contribute to resistance or flow.

Blood follows the path of least resistance. Dilation of the vascular network (through exercise or vasodilator therapy) reduces the resistance of nearby vessels. The flow through the stenotic lesion cannot change, and the arterioles distal to the lesion are maximally dilated. Vessels without disease are not maximally dilated. If dilated—by exercise or **dipyridamole** infusion—the resistance in the nondiseased vessels would decrease while remaining the same in the diseased. With reduced resistance, more blood flows into the now dilated nondiseased vessels. That flow is "stolen" from the diseased vessels. Excess flow is diverted towards the healthy vessels that are now dilating from non-maximal dilation. The diseased vessels cannot dilate further and so get relatively less flow, provoking symptoms.

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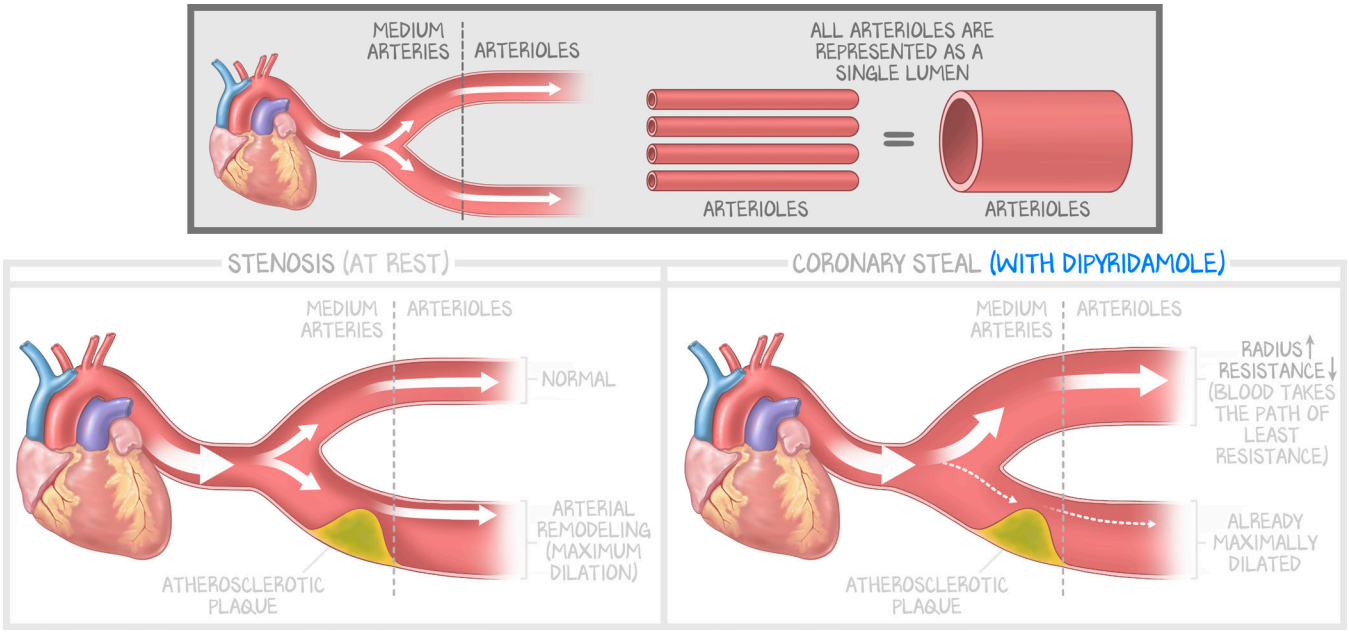

Figure 3.2: Coronary Steal
At rest, the blood flow to the tissue is maximized by maximal vasodilation of the stenotic coronary arteries and relative vasoconstriction of arteries without disease. When a vasodilator is applied to the system, the affected arteries cannot dilate further, but the unaffected arteries can. Therefore, there is a relative drop in resistance in the normal vessels, which steal the perfusion pressure from the diseased vessels, compromising flow and provoking ischemia.

Nitroglycerin does not dilate arteries. A common misconception about nitroglycerin's mechanism of action is that it is an arterial dilator. We've already taught you that nitroglycerin, like all nitrates, is a venodilator, reducing preload and, therefore, myocardial oxygen demand. Even if nitroglycerin were an arterial dilator (it isn't), the diseased vessels are already maximally dilated. Any dilation of the coronary arteries results in less flow through the diseased vessel and would worsen symptoms.

Prinzmetal's Variant Angina = Supply Ischemia without Atherosclerosis

Vasospastic angina is a variant of **supply ischemia** provoked by **coronary artery vasospasm** without the presence of an already compromised lumen. That is, vasospasm that occurs in the absence of an atherosclerotic plaque. We're talking about it here because it is so much less important than acute coronary syndrome that it doesn't deserve a place on the acute coronary syndrome spectrum. However, because this lesson is focused on supply vs. demand ischemia, we wanted to include a concrete example of supply ischemia that is not acute coronary syndrome.

The spasmed coronary artery acutely reduces blood flow. The lumen changes caliber acutely, whereas myocardial oxygen demand does not change, provoking supply ischemia. It is caused by enhanced sympathetic activity and dysfunctional coronary endothelium. This usually presents in younger patients, who, if they were to receive a left heart catheterization, would have normal vasculature. Triggers include things that ramp up vasoconstriction by stimulating α_1 receptors—**cocaine**, **amphetamine**, and **triptans**. Of the three, **triptans are the most relevant**. They are used to treat migraines but absolutely must be avoided in people who have coronary artery disease.

In the case of vasospastic angina not induced by a toxin, there is usually no infarction because vasospasm is temporary. In the case of toxin-induced vasospasm, such as **cocaine chest pain**, the cause of vasospasm is not transient, or transient until the drug wears off which can be too long to save tissue. This can lead to infarction. Cocaine drives sympathetic activity, increasing the heart rate (myocardial

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oxygen demand), increasing afterload (myocardial oxygen demand), and perhaps also inducing vasospasm. The treatment for cocaine chest pain is mostly supportive—oxygen, benzodiazepines to calm the person down, and vasodilators might help. Nitroglycerin and dihydropyridine calcium-channel blockers can help vasodilate the spasm. A commonly tested thing is never to give a patient with cocaine toxicity a β-blocker. Blocking β_1 will slow the heart rate and reduce contractility (reducing myocardial oxygen demand). But blocking β_2 will leave α_1 unopposed, resulting in a catastrophic rise in blood pressure. Routine use of nonselective β-blockers (nadolol and propranolol) is restricted to esophageal varices prophylaxis and stage fright. The β-blockers routinely used in cardiac care block either β_1 only (metoprolol) or β_1 and α_1 combined.

Transition

This lesson was about showing you the see-saw between supply and demand, a slowly growing stable plaque without rupture. The next lesson goes over the medications used to treat chronic stable coronary artery disease. The goals are to reduce the work of the heart, reduce risk factors, and prevent plaque rupture into an acute thrombosis.

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